Studies on the Detoxicating Hormone of the Liver (Yakriton).

82nd Report.

By

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Introduction.

Since the first isolation of yakriton, the detoxicating hormone of the liver, by Prof. Sato, it has been known that it not only detoxicates such endogenous poisons as ammonia,\(^1\) phenol\(^2\) or urea,\(^3\) but also such an exogenous poison as phosphorus,\(^4\) for instance. Further reports from different authors and practicians have shown that yakriton detoxicates very different poisons specifically.

Recently Ouchi\(^5\) of the Eastern Bureau, League of Nations, Singapore, has further widened the therapeutic field of yakriton. He experienced a case of scorpion bite (Liocheles australasiae Fabricius) in a child of 7 years, and used 1 R.A.U. of yakriton in the acutely swollen part of the bite, thereby making several subcutaneous injections (the whole amount being 1 R.A.U.) in the periphery of the swelling. The child’s severe pain stopped abruptly and the swelling subsided remarkably on the next day. Further, Ouchi tried yakriton with success in 6 cases of snake-bite; in these cases he applied the hormone again locally or in the site of the snake bite. He was very interested in the experience and kindly sent a specimen of dried snake

1) A. Sato, Proceedings of the Imperial Academy, 1926, II. No. 9, 518.
5) T. Ouchi, Chiryo-Yakh., 1934, No. 3804, 1.
venom to Prof. Sato, in case he or his laborants should try to perform animal experimentation. The venom he sent was that of the Formosan cobra (Naja naja atra). In the present paper only a preliminary report of the detoxication of the cobra venom through yakriton will be published.

**Method of Experiment.**

1. Animals for experiment. Healthy rabbits were put three times to Sato and Sakurada's liver function test, and only b-classed (low-classed) rabbits were used for the experiment proper.

2. Snake poison and units of yakriton. The dried venom of Formosan cobra was dissolved in distilled water and subcutaneously injected into the interscapular space in an amount of 0.4 mgrms. per kilogram of body weight. About 5 minutes later 1 R.A.U. of yakriton per kilo of body weight was subcutaneously injected.

**Results of Experiment.**

The results of experiment will be shown in the accompanying table.

All the 7 control animals succumbed to the venom, and the time of survival was from 4.5 hours (the minimum) to 8 hours (the maximum). Of the 7 yakriton animals—or the rabbits that received yakriton ther-

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Nos. of rabbits</th>
<th>Body weight in kilos</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exp. 1</td>
<td>(No. 6131)</td>
<td>2.87 (Yakriton animal)</td>
<td>Survived</td>
</tr>
<tr>
<td></td>
<td>(No. 6132)</td>
<td>2.77 (Control animal)</td>
<td>Died after 6 hours</td>
</tr>
<tr>
<td>Exp. 2</td>
<td>(No. 6133)</td>
<td>2.20 (Yakriton animal)</td>
<td>Died after 14 hours</td>
</tr>
<tr>
<td></td>
<td>(No. 6134)</td>
<td>2.66 (Control animal)</td>
<td>Died after 4.5 hours</td>
</tr>
<tr>
<td>Exp. 3</td>
<td>(No. 6135)</td>
<td>3.77 (Yakriton animal)</td>
<td>Died after 15 hours</td>
</tr>
<tr>
<td></td>
<td>(No. 6136)</td>
<td>3.20 (Control animal)</td>
<td>Died after 6.3 hours</td>
</tr>
<tr>
<td>Exp. 4</td>
<td>(No. 6137)</td>
<td>2.30 (Yakriton animal)</td>
<td>Survived</td>
</tr>
<tr>
<td></td>
<td>(No. 6138)</td>
<td>2.54 (Control animal)</td>
<td>Died after 5 hours</td>
</tr>
<tr>
<td>Exp. 5</td>
<td>(No. 6139)</td>
<td>2.94 (Yakriton animal)</td>
<td>Survived</td>
</tr>
<tr>
<td></td>
<td>(No. 6140)</td>
<td>2.47 (Control animal)</td>
<td>Died after 8 hours</td>
</tr>
<tr>
<td>Exp. 6</td>
<td>(No. 6141)</td>
<td>3.09 (Yakriton animal)</td>
<td>Survived</td>
</tr>
<tr>
<td></td>
<td>(No. 6142)</td>
<td>3.15 (Control animal)</td>
<td>Died after 7 hours</td>
</tr>
<tr>
<td>Exp. 7</td>
<td>(No. 6143)</td>
<td>2.76 (Yakriton animal)</td>
<td>Died after 10 hours</td>
</tr>
<tr>
<td></td>
<td>(No. 6144)</td>
<td>2.96 (Control animal)</td>
<td>Died after 6 hours</td>
</tr>
</tbody>
</table>

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6) A. Sato and H. Sakurada, Tohoku J. Exp. Med., 1927, 8, 347.
apy once—4 rabbits outlived the poisoning and remained alive. And even the three rabbits which succumbed to the snake venom survived the poisoning for from 10 hours to about 15 hours, about twice as long as the controls did.

The condition of the animals after the administration of the snake venom was almost that already described by Iwase. As death drew near, rabbits hanged the head downwards, kept the fore part of the thorax near to the floor and lay then flat on the floor with one side of the head on it. A stridor would occur and respiration became very dyspnoic.

**Comment.**

The mortality of human beings due to Formosan cobra (Naja naja atra) is according to Yamaguchi and according to Miyamoto. It will thus be seen that it is a very poisonous venom. The minimum lethal dose for rabbits is reported to be from 0.1 to 0.5 mgrms. per kilo of body weight. According to Iwase, a subcutaneous injection of 0.5 mgrms. of that snake venom into the rabbit causes no symptom within one hour, but near the end of 2 hours paralytic symptoms will occur, and the head will hang downwards, the fore part of the thorax come near to the floor, until the animal lies flat on the floor with its head inclined. Meanwhile, the paralysis will affect fore legs, but hind legs will still remain intact. Later these will be paralysed and gait become impossible, until dyspnoea becomes severer and death ensues in 2½ hours after the injection. Immediate autopsy will show that the heart beats still for a short time, but will suddenly stop beating. The vessels of the visceral organs, especially mesenteric ones, are filled as if crammed, and the liver and the inner walls of the trachea are injected. Except these finding, there is, according to him, no special feature seen at the autopsy. The subcutaneous injection of 0.1 mgrm. will, according to him, cause no symptoms and the rabbit will remain alive.

Kanisawa is of the opinion that the acute death caused by Naja naja atra is on account of the respiratory paralysis due to the large content of "neurotoxin" in the venom. Yamaguchi investi-
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gated the effects of the poisons of different snakes native in Formosa and found that the venom of Naja naja atra effects mucosa most severely. He states that the venoms of the other snakes will not, if perorally used, kill animals, even though a large amount of it is daily administered, but as to the venom of Naja naja atra, guinea-pigs one to three days after birth, will be killed if a dose larger than ten times as large as sufficient to kill them by subcutaneous injection of the poison is used.

The local treatment for the snake bite is cutting of the skin in the neighbourhood of the wound, an application of potassium permanganate solution, of hydrogen peroxid, Lugol's solution, etc. And the general treatment is the use of heart stimulants, physiological saline, oxygen inhalation, and especially specific antitoxic sera. As to the specific sera Yama
guchi states that much more antitoxin is necessary for the neutralisation of the venom injected into the body than for the neutralisation of it in vitro. If one attempts to rescue an animal which has just received an injection of the venom in a certain amount, by means of the antitoxin injected in another site, then the amount of the antitoxin should be 4 times as large as that which is the minimum amount necessary for neutralizing the same amount of the venom in vivo, provided the mixture is used at once.

By way of appendix, Hashimoto reported of an efficacy of vitamin B against cobra poison, and some authors report of the therapeutical application of snake venom for some diseases.

Conclusion.

The result of my preliminary experiment will lead to the following conclusion:—

Yakriton, the detoxicating hormone of the liver, which is reported clinically to be specifically efficacious in the treatment of the snake bite, has been shown to be effectual in the detoxication of rabbits poisoned with the venom of Formosan cobra (Naja naja atra). It is especially interesting to note that yakriton, which has nothing to do with antitoxin or antitoxic sera, will detoxicate snake venom quite specifically.

12) K. Yamaguchi, Contributions from the Department of Hygiene, Government Research Institute, Formosa. No. 1 (1921).
13) T. Hashimoto, Taiwan Igaku-kai Zasshi, 1934, 38, 873.